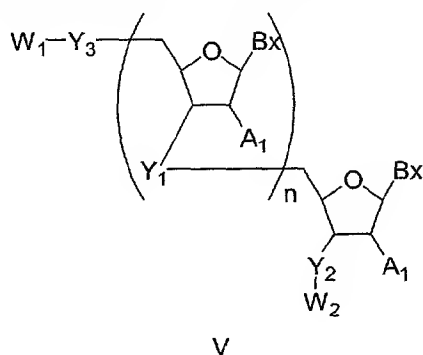


WHAT IS CLAIMED IS:

1. An oligomeric compound of formula V:



- 5 wherein:

n is from 3 to about 50;

each Y₁ is, independently, an internucleoside linking group;

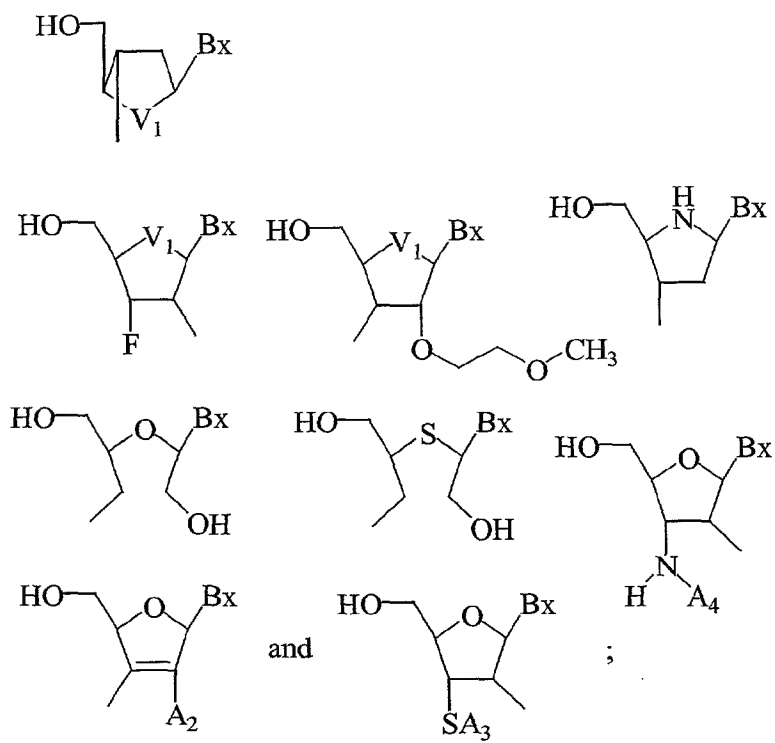
Y₂ is oxygen or an internucleoside linking group;

Y₃ is oxygen or an internucleoside linking group;

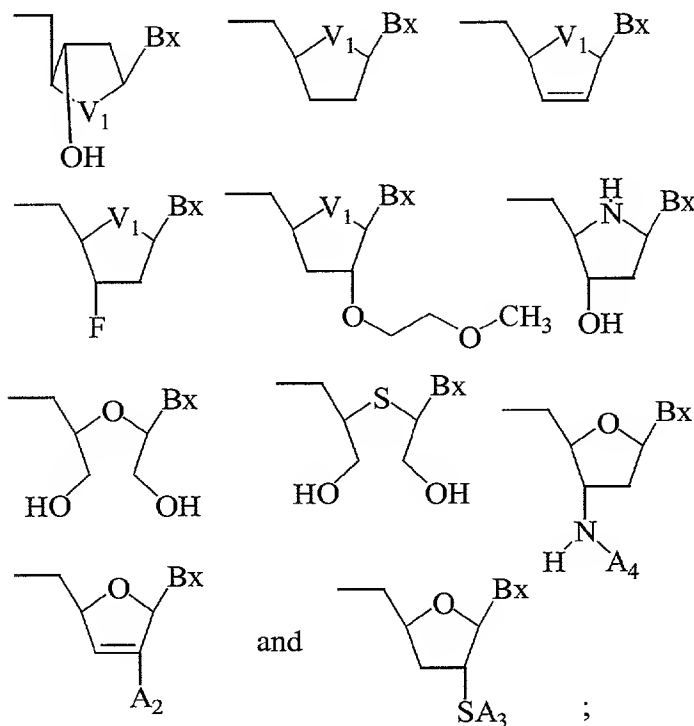
- 10 each Bx is an optionally protected heterocyclic base moiety;

each A₁ is, independently, hydrogen or a sugar substituent group;

W_1 is hydrogen, a hydroxyl protecting group or a modified nucleoside selected from the group consisting of



W₂ is hydrogen, a hydroxyl protecting group or a modified nucleoside selected from the group consisting of



5

each A₂ is, independently, alkyl, alkenyl, alkynyl, aryl, alkaryl, O-alkyl, O-aryl, amino, substituted amino, -SH, -SA₃, thioether, F, or morpholino;

each A₃ is, independently, H, a sulfur protecting group, aryl, alkaryl, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl, substituted or unsubstituted C₂-C₁₀ alkynyl, or alkaryl, wherein said substitution is OA₅ or SA₅;

each A₄ is, independently, H, a nitrogen protecting group, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl, substituted or unsubstituted C₂-C₁₀ alkynyl, or alkaryl, wherein said substitution is OA₅ or SA₅;

each A₅ is, independently, hydrogen, C₁-C₁₀ alkyl, cycloalkyl or aryl;

each V₁ is, independently, O or S;

wherein at least one of W₁ and W₂ is not hydrogen or a hydroxyl protecting group and at least one internucleoside linking group is not a phosphodiester linking group.

20

2. The oligomeric compound of claim 1 wherein n is from about 8 to about 30.

3. The oligomeric compound of claim 1 wherein n is from about 15 to about 25.

4. The oligomeric compound of claim 1 wherein each of said internucleoside linking groups is a phosphorus containing internucleoside linking group.

5. The oligomeric compound of claim 4 wherein each of said phosphorus containing internucleoside linking groups is independently selected from the group consisting of phosphodiester, phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl phosphonate, alkyl phosphonate, 5'-alkylene phosphonate, chiral phosphonate, phosphinate, phosphoramidate, 3'-amino phosphoramidate, aminoalkylphosphoramidate, thionophosphoramidate, thionoalkylphosphonate, thionoalkylphosphotriester, selenophosphate and boranophosphate.

6. The oligomeric compound of claim 5 wherein none of said internucleoside linking groups is a phosphodiester internucleoside linking group.

7. The oligomeric compound of claim 5 wherein greater than 90% of said internucleoside linking groups are phosphorothioate internucleoside linking groups.

8. The oligomeric compound of claim 1 wherein at least one of said internucleoside linking groups is a non-phosphorus containing internucleoside linking group.

9. The oligomeric compound of claim 8 wherein greater than 90% of said internucleoside linking groups are non-phosphorus containing internucleoside linking groups.

10. The oligomeric compound of claim 9 wherein each of said non-phosphorus containing internucleoside linking groups is, independently, selected from the group consisting of morpholino, siloxane, sulfide, sulfoxide, sulfone, formacetyl,

thioformacetyl, methylene formacetyl, thioformacetyl, sulfamate, methyleneimino, methylenehydrazino, sulfonate, sulfonamide, and amide.

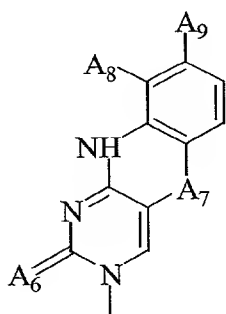
11. The oligomeric compound of claim 10 wherein each of said internucleoside
5 linking groups is, independently, $-\text{CH}_2\text{-NH-O-CH}_2-$, $-\text{CH}_2\text{-N(CH}_3\text{)-O-CH}_2-$ or $-\text{CH}_2\text{-O-N(CH}_3\text{)-CH}_2-$, $-\text{CH}_2\text{-N(CH}_3\text{)-N(CH}_3\text{)-CH}_2-$ or $-\text{O-N(CH}_3\text{)-CH}_2\text{-CH}_2-$.

12. The oligomeric compound of claim 1 wherein said oligomeric compound is a
10 gapmer, hemimer or inverted gapmer.

- 13 The oligomeric compound of claim 12 comprising at least one $2'\text{-O-CH}_2\text{CH}_2\text{-O-CH}_3$ sugar substituent group in at least one region of said gapmer, hemimer or
inverted gapmer.

14. The oligomeric compound of claim 1 comprising at least one nucleoside
15 wherein Bx is a polycyclic heterocyclic base moiety.

15. The oligomeric compound of claim 14 wherein each of said polycyclic
heterocyclic base moieties is, independently, of the formula:

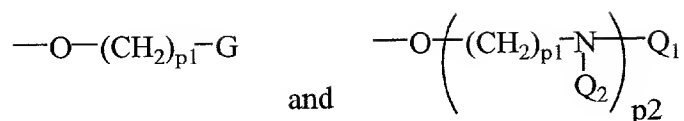


wherein

A₆ is O or S;

- 25 A₇ is CH₂, N-CH₃, O or S;

each A₈ and A₉ is hydrogen or one of A₈ and A₉ is hydrogen and the other of
A₈ and A₉ is selected from the group consisting of



wherein:

G is -CN, -OA₁₀, -SA₁₀, -N(H)A₁₀, -ON(H)A₁₀ or -C(=NH)N(H)A₁₀;

Q₁ is H, -NHA₁₀, -C(=O)N(H)A₁₀, -C(=S)N(H)A₁₀ or -

5 C(=NH)N(H)A₁₀,

each Q₂ is, independently, H or Pg;

A₁₀ is H, Pg, substituted or unsubstituted C₁-C₁₀ alkyl, acetyl, benzyl, -(CH₂)_{p3}NH₂, -(CH₂)_{p3}N(H)Pg, a D or L α-amino acid, or a peptide derived from D, L or racemic α-amino acids;

10 Pg is a nitrogen, oxygen or thiol protecting group;

each p₁ is, independently, from 2 to about 6;

p₂ is from 1 to about 3; and

p₃ is from 1 to about 4.

15 16. The oligomeric compound of claim 1 wherein Y₃ is an internucleoside linking group and W₁ is a modified nucleoside.

17. The oligomeric compound of claim 1 wherein Y₂ is an internucleoside linking group and W₂ is a modified nucleoside.

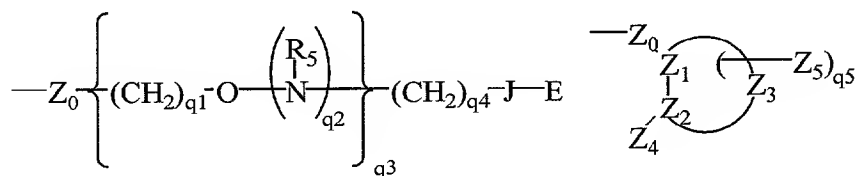
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18. The oligomeric compound of claim 1 wherein each of said B_x is independently selected from the group consisting of adeninyl, guaninyl, thyminyl, cytosinyl, uracilyl, 5-methylcytosinyl (5-me-C), 5-hydroxymethyl cytosinyl, xanthinyl, hypoxanthinyl, 2-aminoadeninyl, alkyl derivatives of adeninyl and
25 guaninyl, 2-thiouracilyl, 2-thiothyminyl, 2-thiocytosinyl, 5-halouracilyl, 5-halocytosinyl, 5-propynyl uracilyl, 5-propynyl cytosinyl, 6-azo uracilyl, 6-azo cytosinyl, 6-azo thyminyl, 5-uracilyl (pseudouracil), 4-thiouracilyl, 8-substituted adeninyls and guaninyls, 5-substituted uracilyls and cytosinyls, 7-methylguaninyl, 7-methyladeninyl, 8-azaguaninyl, 8-azaadeninyl, 7-deazaguaninyl, 7-deazaadeninyl, 3-
30 deazaguaninyl and 3-deazaadeninyl.

19. The oligomeric compound of claim 1 wherein each sugar substituent group is, independently, C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₅-C₂₀ aryl, -O-alkyl, -O-alkenyl, -O-alkynyl, -O-alkylamino, -O-alkylalkoxy, -O-alkylaminoalkyl, -O-alkylimidazole, -OH, -SH, -S-alkyl, -S-alkenyl, -S-alkynyl, -N(H)-alkyl, -N(H)-alkenyl, -N(H)-alkynyl, -N(alkyl)₂, -O-aryl, -S-aryl, -NH-aryl, -O-aralkyl, -S-aralkyl, -N(H)-aralkyl, phthalimido (attached at N), halogen, amino, keto (-C(=O)-R), carboxyl (-C(=O)OH), nitro (-NO₂), nitroso (-N=O), cyano (-CN), trifluoromethyl (-CF₃), trifluoromethoxy (-O-CF₃), imidazole, azido (-N₃), hydrazino (-N(H)-NH₂), aminooxy (-O-NH₂), isocyanato (-N=C=O), sulfoxide (-S(=O)-R), sulfone (-S(=O)₂-R), disulfide (-S-S-R), silyl, heterocyclyl, carbocyclyl, an intercalator, a reporter group, a conjugate group, polyamine, polyamide, polyalkylene glycol or a polyether of the formula (-O-alkyl)_m, where m is 1 to about 10;

wherein each R is, independently, hydrogen, a protecting group or substituted or unsubstituted alkyl, alkenyl, or alkynyl wherein the substituent groups are selected from haloalkyl, alkenyl, alkoxy, thioalkoxy, haloalkoxy or aryl as well as halogen, hydroxyl, amino, azido, carboxy, cyano, nitro, mercapto, a sulfide group, a sulfonyl group and a sulfoxide group;

or each sugar substituent group has one of formula I or II:



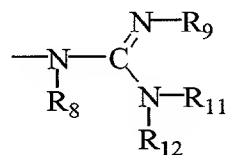
wherein:

Z₀ is O, S or NH;

J is a single bond, O or C(=O);

E is C₁-C₁₀ alkyl, N(R₅)(R₆), N(R₅)(R₇), N=C(R_{5a})(R_{6a}), N=C(R_{5a})(R_{7a}) or has

formula III;



III

each R_8 , R_9 , R_{11} and R_{12} is, independently, hydrogen, $C(O)R_{13}$, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group or a conjugate group, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl;

or optionally, R_{11} and R_{12} , together form a phthalimido moiety with the nitrogen atom to which they are attached;

each R_{13} is, independently, substituted or unsubstituted C_1 - C_{10} alkyl, trifluoromethyl, cyanoethoxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)-ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, iso-butyryl, phenyl or aryl;

R_5 is hydrogen, a nitrogen protecting group or -T-L,

R_{5a} is hydrogen, a nitrogen protecting group or -T-L,

T is a bond or a linking moiety;

L is a chemical functional group, a conjugate group or a solid support medium;

each R_6 and R_7 is, independently, H, a nitrogen protecting group, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl, alkynyl; NH_3^+ , $N(R_{14})(R_{15})$, guanidino and acyl where said acyl is an acid amide or an ester;

or R_6 and R_7 , together, are a nitrogen protecting group, are joined in a ring structure that optionally includes an additional heteroatom selected from N and O or are a chemical functional group;

each R_{14} and R_{15} is, independently, H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{14} and R_{15} , together, are a nitrogen protecting group;

or R_{14} and R_{15} are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

Z_4 is OX, SX, or $N(X)_2$;

each X is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, $C(=NH)N(H)R_{16}$, $C(=O)N(H)R_{16}$ or $OC(=O)N(H)R_{16}$;

R_{16} is H or C_1 - C_8 alkyl;

Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 heteroatoms wherein said heteroatoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated

5 heterocyclic;

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(R_5)(R_6)OR_5$, halo, SR_5 or CN;

each q_1 is, independently, an integer from 1 to 10;

10 each q_2 is, independently, 0 or 1;

q_3 is 0 or an integer from 1 to 10;

q_4 is an integer from 1 to 10;

q_5 is from 0, 1 or 2; and

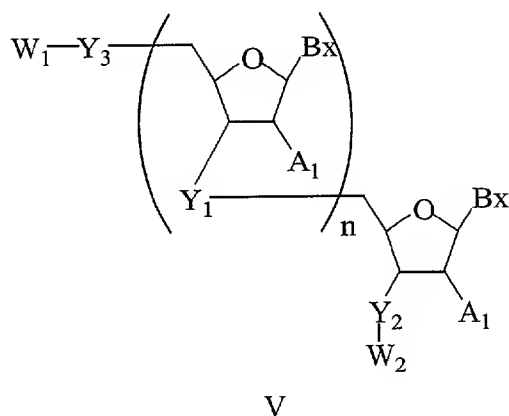
provided that when q_3 is 0, q_4 is greater than 1.

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20. The oligomeric compound of Claim 19 wherein each of said sugar substituent groups is, independently, $-O-CH_2CH_2OCH_3$, $-O(CH_2)_2ON(CH_3)_2$, $-O-(CH_2)_2-O-(CH_2)_2-N(CH_3)_2$, $-O-CH_3$, $-OCH_2CH_2CH_2NH_2$, $-CH_2-CH=CH_2$, or fluoro.

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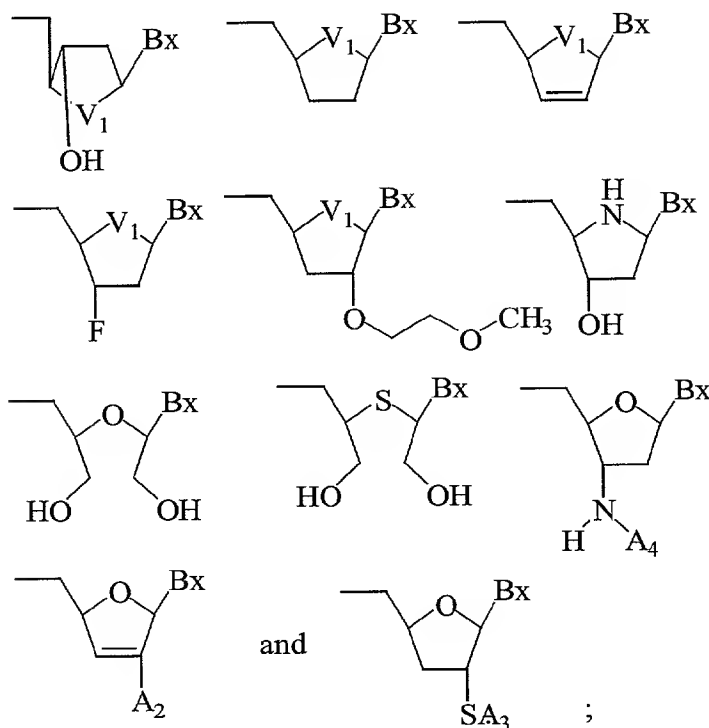
21. A method of enhancing the nuclease resistance of an oligomeric compound comprising providing at least one modified nucleoside at either the 3' or 5' terminus of said oligomeric compound to give a modified oligomeric compound of formula V:



25 wherein:

n is from 3 to about 50;

W_2 is hydrogen, a hydroxyl protecting group or a modified nucleoside selected from the group consisting of



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each A_2 is, independently, alkyl, alkenyl, alkynyl, aryl, alkaryl, O-alkyl, O-aryl, amino, substituted amino, -SH, -SA₃, thioether, F, or morpholino;

each A_3 is, independently, H, a sulfur protecting group, aryl, alkaryl, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl, substituted or unsubstituted C₂-C₁₀ alkynyl, or alkaryl, wherein said substitution is OA₅ or SA₅;

each A_4 is, independently, H, a nitrogen protecting group, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl, substituted or unsubstituted C₂-C₁₀ alkynyl, or alkaryl, wherein said substitution is OA₅ or SA₅;

each A_5 is, independently, hydrogen, C₁-C₁₀ alkyl, cycloalkyl or aryl;

each V_1 is, independently, O or S;

wherein at least one of W_1 and W_2 is not hydrogen or a hydroxyl protecting group.

20

22. The method of claim 21 wherein n is from about 8 to about 30.

23. The method of claim 21 wherein n is from about 15 to about 25.

5 24. The method of claim 21 wherein each of said internucleoside linking groups is a phosphorus-containing internucleoside linking group.

25. The method of claim 24 wherein each of said phosphorus containing
internucleoside linking groups is selected from the group consisting of
10 phosphodiester, phosphorothioate, chiral phosphorothioate, phosphorodithioate,
phosphotriester, aminoalkylphosphotriester, methyl phosphonate, alkyl phosphonate,
5'-alkylene phosphonate, chiral phosphonate, phosphinate, phosphoramidate, 3'-
amino phosphoramidate, aminoalkylphosphoramidate, thionophosphoramidate,
thionoalkylphosphonate, thionoalkylphosphotriester, selenophosphate and
15 boranophosphate.

26. The method of claim 25 wherein none of said internucleoside linking groups is a phosphodiester internucleoside linking group.

20 27. The method of claim 25 wherein greater than 90% of said internucleoside linking groups are phosphodiester internucleoside linking groups.

28. The method of claim 21 wherein at least one of said internucleoside linking groups is a non-phosphorus containing internucleoside linking group.

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29. The method of claim 28 wherein greater than 90% of said internucleoside linking groups are non-phosphorus containing internucleoside linking groups.

30. The method of claim 29 wherein each of said non-phosphorus containing
30 internucleoside linking groups is, independently, selected from the group consisting of
morpholino, siloxane, sulfide, sulfoxide, sulfone, formacetyl, thioformacetyl,
methylene formacetyl, thioformacetyl, sulfamate, methyleneimino,
methylenehydrazino, sulfonate, sulfonamide, and amide.

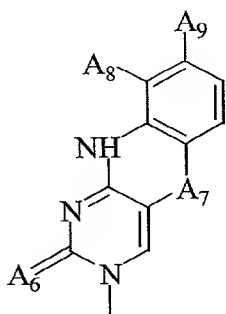
31. The method of claim 30 wherein each of said internucleoside linking groups is, independently, $-\text{CH}_2-\text{NH}-\text{O}-\text{CH}_2-$, $-\text{CH}_2-\text{N}(\text{CH}_3)-\text{O}-\text{CH}_2-$, $-\text{CH}_2-\text{O}-\text{N}(\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{N}(\text{CH}_3)-\text{N}(\text{CH}_3)-\text{CH}_2-$ or $-\text{O}-\text{N}(\text{CH}_3)-\text{CH}_2-\text{CH}_2-$.

5 32. The method of claim 21 wherein said oligomeric compound is a gapmer, hemimer or inverted gapmer.

33. The method of claim 32 wherein the oligomeric compound comprises at least one 2'-O-CH₂CH₂-O-CH₃ sugar substituent group in at least one region of said
10 gapmer, hemimer or inverted gapmer.

34. The method of claim 21 comprising at least one nucleoside wherein Bx is a polycyclic heterocyclic base moiety.

15 35. The method of claim 34 wherein each of said polycyclic heterocyclic base moieties is, independently, of the formula:



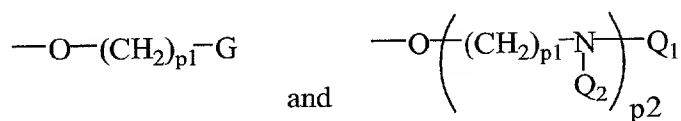
20 wherein

A₆ is O or S;

A₇ is CH₂, N-CH₃, O or S;

each A₈ and A₉ is hydrogen or one of A₈ and A₉ is hydrogen and the other of A₈ and A₉ is selected from the group consisting of:

25



wherein:

wherein:

G is -CN, -OA₁₀, -SA₁₀, -N(H)A₁₀, -ON(H)A₁₀ or -C(=NH)N(H)A₁₀;

5 Q₁ is H, -NHA₁₀, -C(=O)N(H)A₁₀, -C(=S)N(H)A₁₀ or -C(=NH)N(H)-
A₁₀;

each Q₂ is, independently, H or Pg;

A₁₀ is H, Pg, substituted or unsubstituted C₁-C₁₀ alkyl, acetyl, benzyl,
-(CH₂)_{p3}NH₂, -(CH₂)_{p3}N(H)Pg, a D or L α-amino acid, or a peptide derived from D, L
10 or racemic α-amino acids;

Pg is a nitrogen, oxygen or thiol protecting group;

each p₁ is, independently, from 2 to about 6;

p₂ is from 1 to about 3; and

p₃ is from 1 to about 4.

15 36. The method of claim 21 wherein Y₃ is an internucleoside linking group and
W₁ is a modified nucleoside.

20 37. The method of claim 21 wherein Y₂ is an internucleoside linking group and
W₂ is a modified nucleoside.

38. The method of claim 21 wherein each of said B_x is independently selected
from the group consisting of adeninyl, guaninyl, thyminyl, cytosinyl, uracilyl, 5-
methylcytosinyl (5-me-C), 5-hydroxymethyl cytosinyl, xanthinyl, hypoxanthinyl, 2-
25 aminoadeninyl, alkyl derivatives of adeninyl and guaninyl, 2-thiouracilyl, 2-
thiothyminyl, 2-thiocytosinyl, 5-halouracilyl, 5-halocytosinyl, 5-propynyl uracilyl, 5-
propynyl cytosinyl, 6-azo uracilyl, 6-azo cytosinyl, 6-azo thyminyl, 5-uracilyl
(pseudouracil), 4-thiouracilyl, 8-substituted adeninyls and guaninyls, 5-substituted
uracilyls and cytosinyls, 7-methylguaninyl, 7-methyladeninyl, 8-azaguaninyl, 8-
30 azaadeninyl, 7-deazaguaninyl, 7-deazaadeninyl, 3-deazaguaninyl and 3-
deazaadeninyl.

each R_8 , R_9 , R_{11} and R_{12} is, independently, hydrogen, $C(O)R_{13}$, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group or a conjugate group, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl;

or optionally, R_{11} and R_{12} , together form a phthalimido moiety with the nitrogen atom to which they are attached;

each R_{13} is, independently, substituted or unsubstituted C_1 - C_{10} alkyl, trifluoromethyl, cyanoethyloxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)-ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, iso-butyryl, phenyl or aryl;

R_5 is hydrogen, a nitrogen protecting group or -T-L,

R_{5a} is hydrogen, a nitrogen protecting group or -T-L,

T is a bond or a linking moiety;

L is a chemical functional group, a conjugate group or a solid support medium;

each R_6 and R_7 is, independently, H, a nitrogen protecting group, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl, alkynyl; NH_3^+ , $N(R_{14})(R_{15})$, guanidino and acyl where said acyl is an acid amide or an ester;

or R_6 and R_7 , together, are a nitrogen protecting group, are joined in a ring structure that optionally includes an additional heteroatom selected from N and O or are a chemical functional group;

each R_{14} and R_{15} is, independently, H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{14} and R_{15} , together, are a nitrogen protecting group;

or R_{14} and R_{15} are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

Z_4 is OX, SX, or $N(X)_2$;

each X is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, $C(=NH)N(H)R_{16}$, $C(=O)N(H)R_{16}$ or $OC(=O)N(H)R_{16}$;

R_{16} is H or C_1 - C_8 alkyl;

Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 heteroatoms wherein said heteroatoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated

5 heterocyclic;

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(R_5)(R_6)OR_5$, halo, SR_5 or CN;

each q_1 is, independently, an integer from 1 to 10;

10 each q_2 is, independently, 0 or 1;

q_3 is 0 or an integer from 1 to 10;

q_4 is an integer from 1 to 10;

q_5 is from 0, 1 or 2; and

provided that when q_3 is 0, q_4 is greater than 1.

15

40. The method of Claim 39 wherein each of said sugar substituent groups is, independently, $-O-CH_2CH_2OCH_3$, $-O(CH_2)_2ON(CH_3)_2$, $-O-(CH_2)_2-O-(CH_2)_2-N(CH_3)_2$, $-O-CH_3$, $-OCH_2CH_2CH_2NH_2$, $-CH_2-CH=CH_2$ or fluoro.